Carcinoma of the Thyroid in Surgical and Postmortem Material

Analysis of 300 Cases at Autopsy and Literature Review

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IN VIEW of the clinical significance of carcinoma of the thyroid, it is surprising that so little work has been done to establish its true incidence. Many authors [11, 27, 36, 47, 64] believe that this is a potentially lethal disease and quote high mortality figures if patients are followed for a sufficiently long period. Others, citing the high incidence of thyroid cancer in surgical statistics and the considerably lower incidence at postmortem examination,[17, 49, 56, 57] claim that patients with this neoplasm are rarely killed by it and that it is only seldom a problem of grave clinical significance. A recent statistical analysis of thyroid cancer incidence in New York State [7] reveals that the incidence for this tumor has more than doubled from 1941 to 1962, representing an increase in incidence larger than for malignant tumors of any other site except lung.

We believe that a major part of the problem is lack of uniform interpretation of autopsy material. One reason for this is the frequently inadequate examination of thyroid at routine postmortem examinations. In an Armed Forces Institute of Pathology survey of 117 protocols of autopsies on patients without known thyroid disease, only 38 per cent included reference to the thyroid.[47] Of 2,185 autopsies reported from three Boston Hospitals, only 1,371 (62.8%) included examination of the thyroid.[45] Even when thyroid is inspected grossly, often no section or perhaps a single section is submitted for microscopic examination. The present study is based on 300 thyroid glands obtained at consecutive postmortem examinations in a large community hospital.

Materials and Methods

During the period of study (May 1964 through March 1965), 530 autopsies were performed at the Yale-New Haven Hospital. Autopsies on patients under the age of 20 years were not included nor (by necessity) were those in which autopsy permission did not include neck organs; when these cases were eliminated, 300 otherwise unselected cases were available for examination. There were 183 males and 117 females. The age range is listed in Figure 1; 251 of the 300 subjects were over 50 years of age at time of death.

Each of the thyroid glands was removed in toto by the resident performing the autopsy, weighed and given intact to us.

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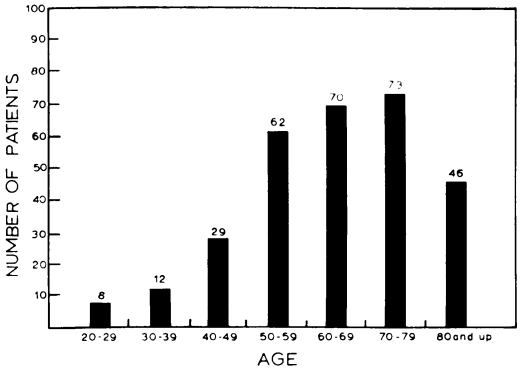

FIG. 1. Distribution of patients by age at death. The number of patients in each group are represented by the black bars. The actual number in each group is shown at the top of each bar.

After fixation in 10% formalin solution, the thyroids were inspected and palpated, and each was sectioned manually at intervals of 2–3 mm. All grossly visible lesions were noted and many were photographed. Sections of all visible gross lesions were submitted to microscopic examination, including all nodules regardless of size; in thyroids with few or no such lesions, a minimum of one section per 5 grams of tissue was submitted. All sections were stained with Hematoxylin and eosin, and with other stains where indicated. Both authors examined sections of each thyroid independently, and in the few instances in which we did not immediately agree on a diagnosis, more section or stains were obtained and all material was reviewed together.

Observations and Discussion

Classification. Final diagnoses affixed to the 300 thyroid glands studied are listed in Table 1. There are more than 300 diagnoses, as several thyroids contained more than one lesion. Our diagnostic category of "adenomatous thyroid" includes those lesions described by other pathologists as "adenomatous goiter" and "multinodular colloid goiter" because many of these glands were normal or small sized and by definition not goitrous. By "diffuse goiter" we refer to any gland weighing over 35 grams and not showing criteria for other diagnostic categories; this weight was chosen because of almost universal acceptance by Western Hemisphere authors [21, 24, 28, 30] as the upper limit of weight of normal thyroid. We made no attempt to distinguish between glands containing foci of hyperplasia and those not containing such foci. Diagnoses of adenoma and carcinoma were made in accordance with criteria established by Warren and Meissner [59] and widely accepted by pathologists.

Weight. The average weight of thyroid glands in any series depends largely upon the region from which the population is drawn. Almost all of our subjects were residents of Connecticut, a "nongoitrous" area, and the majority had been born in this region. The average weight of all thyroids was 28.04 grams. Comparable weights in other locations are 29.1 grams in Colorado,[30] 23.2 grams in Kansas,[24] 23.2 grams in Minnesota,[24] and 39 grams in Bern.[24] Sixty-five glands (21.7%) weighed over 35 grams, the weight accepted by most authors [21, 22, 24, 30] as the upper limit of normal; the average weight of these 65 glands was 60.17 grams, the heaviest (a substernal goiter) weighing 440 grams. An almost identical percentage of Hull's [30] specimens in Colorado (21.3%) weighed more than 35 grams and were thus by definition goitrous, as compared with 18.4% of Hellwig's [24] in Kansas, 8.1% of these of Hazard and Kaufman [22] in Cleveland, and 8.2% of the thyroids in Jamaica examined by Harland.[21] After elimination of 65 goitrous glands, the average weight of the remaining 235 was 19.50 grams, comparing with 19.6 grams in Colorado and 17 grams in Jamaica.

Diagnoses for thyroids weighing over 35 grams are listed in Table 2. Adenomatous thyroids in this group (true adenomatous

TABLE 1. *Final Diagnoses for 300 Thyroids*

	Number		Per Cent	
Thyroiditis	10		3.3	
Acute		1		0.3
Subacute		1		1.7
Chronic lymphocytic		5		1.7
Hashimoto's struma		3		1.0
Atrophy and/or fibrosis	24		8.0	
Diffuse goiter with or without hyperplasia	12		4.0	
Adenomatous thyroid with or without hyperplasia	150		50.0	
Neoplasms	33		11.0	
Benign adenoma		9		2.7
Other benign tumor (Sclerosing hemangioma)		1		0.3
Carcinoma (primary)		8		2.7
Metastatic malignant tumors		15		5.0
Normal thyroid	84		28.0	
Total	313		104.3*	

* More than one diagnosis applicable to several cases.

TABLE 2. *Diagnoses for 65 Goitrous Glands (Weight > 35 grams)*

Adenomatous thyroid	47
Diffuse goiter	12
Metastatic malignancy	4
Adenoma	3
Primary carcinoma	2
Thyroiditis	2
Atrophy and fibrosis	1
	71

TABLE 3. *Final Diagnosis in 19 Cases with Grossly Single Nodules*

Carcinoma	2
Adenoma	4
Adenomatous thyroid	10
Thyroiditis	1
Focal hyperplasia	1
Intraglandular normal parathyroid	1

goiters) and diffuse goiters were analyzed separately, and ages and sex incidence were similar to those of the entire series of 300 cases. 71.2% of goitrous patients were males, as were 61.0% of the entire series; this difference was not significant, and should be considered in the light of the fact that thyroids from males have been reported to be heavier than,[30] lighter than,[39] and essentially the same weight as [22] those from females. 13.5% of goitrous glands were from patients under 50 years of age and 20.0% over 80 years, as compared with 16.3% and 15.3%, respectively, for the entire series—again not a significant difference. Thus, we found little evidence to support the concept [24,30,39] that thyroid weight decreases with advancing age.

Nodules. A nodule was defined as any circumscribed region in the thyroid that was grossly distinct from surrounding thyroid tissue, whether or not the region was encapsulated. By these criteria, 158 glands (52.7%) contained one or more nodules; 72 (45.6%) contained at least one nodule 1 cm. or greater in diameter (and therefore presumably clinically palpable if superficial), while 86 (54.4%) had only nodules smaller than 1 cm. Nineteen thyroids contained gross single nodules (after sectioning of the gland but before microscopic examination), an incidence of 6.3% of all glands and 12.0% of all nodular glands. Diagnoses in these 19 are listed in Table 3; the chance of a single nodule being a neoplasm (benign or malignant) was 31.6%, almost three times the incidence of neoplasms in the entire series, while 10.5% of single nodules were diagnosed as thyroid carcinoma, almost four times the incidence in the entire series. While these latter figures tend to confirm an often-quoted trend, they are of little significance because of the small number of cases involved.

The incidence of thyroid nodules has attracted the attention of many clinicians and pathologists. Since the percentage of nodular goiters operated upon is high and that of diffuse goiters is low, most surgical series cite a high incidence of nodules. On the other hand, that most thyroid nodules are either too small or too deeply situated to be palpable accounts for the low incidence reported in patients not operated upon. Thus, in a study [55] of routine physical

TABLE 4. *Reported Incidences of Cancer in Surgically Removed Thyroids: Literature Review*

	% All Nodular Goiter	% of Nontoxic Nodular Goiter	% Toxic Nodular Goiter	% Toxic Diffuse Goiter	% Multinodular Nontoxic Goiter	% Thyroids with Clinically Palpable Single Nodules	% Thyroids with Anatomically Verified Single Nodules
Beahrs, Pemberton and Black[1]	4.8	7.5	1.0	0.5			
Beal, Scholnick and Stevens[2]						4.7	
Bowens and Vander[5]	22.9						
Cattell and Colcock[8]	9.1						33.3
Cavanagh[9]	7.0				5.7	10.0	
Coffey, Amoroso and Mazzara[10]	11.5*				6.6*	21.7*	
Cole, Majarakis and Slaughter[11]		17.2					
Cole, Slaughter and Rossiter[12]	7.2	17.1			11.0	24.0	
Cope *et al*[13]						19	
Crile and Dempsey[16]	5.6	10.9				24.5	
Freeman[18]	17						
Greene, Piercy and Singer[20]					8	13	
Hinton and Lord[26]	7.6*						
Horn *et al*.[28]	5.4						
Horrilleno and Lahoz[29]					14.41	14.19	
Lahey and Hare[33]			0.54		0.62	10.04	
Miller[35]		3.7*					
Pigott and Braund[40]						15.5	
Sokal[50]			0.94**				
Tellem, Stahl and Meranze[53]					7	13	18
Veith *et al*.[57]		9					
Ward[58]	4.8						
Watt and Foushee[60]	1						
Williams, Davis and Kiely[61]							14.6
Willis[62]		4.6	1.0		3.7		10.7
Zimmerman[64]	4.5						

* % of clinically benign lesions—obvious cancers excluded.
** Summary of 5,011 cases from several series.

examination of 5,234 persons, 99 palpable solitary nodules were detected, an incidence of 1.9%; however, since other studies [2, 9, 10, 31, 44] indicate that up to 50% of thyroids thought clinically to harbor single nodules contain at pathologic examination multiple nodules, this figure should probably be reduced to 1%, considerably smaller than the incidence of single nodules of 6.3% in the present series. Similarly, the clinically detected incidence of nontoxic nodular goiter of 3% quoted by Sokal [52] is considerably below that ascertained by pathologic study. The incidence of nodules in thyroid glands obtained at autopsy has varied, but always has been higher than reported from physical examinations. Autopsy series cite incidences of 14.9%,[21] 26.3%,[39] 40.4%,[14] 42.4%,[22] 52.5%,[37, 38] 57% [42] and 64.6%.[30] The incidence of pathologically verified single nodules has been 10.9%,[30] 11.9%,[37] 12.0% [22] and 15.2% [42] of all glands examined. Including the present series, the average incidence of multiple nodules is about 45–50% and of single nodules 10–12%.

Carcinoma. Despite agreement about the incidence of thyroid nodules, significance with regard to cancer and the incidence of cancer itself have been subjects of disagreement. Table 4 lists reported incidences of malignant lesions in surgically removed thyroids in 26 series from various institutions. Differences among these figures are due to lack of uniform criteria for selection of patients for operation and differences in patient material in the reporting institutions. Patients reported by Bowens and Vander [5] and Pigott and Braund [40] come from cancer clinics and would be expected to have a high incidence of malignant disease. Only Miller,[35] Hinton and Lord,[26] and Coffey, Amoroso and Mazzara [10] eliminate obviously malignant lesions from consideration in attempts to assess the malignant potential of a nodular thyroid. Since suspiciously malignant lesions are most likely to be operated upon, the figures of Cole,[11,12] Freeman,[18] and Watt and Foushee [60] are the least subject to such prejudice since all patients with nodular thyroids were subjected to operation regardless of the preoperative diagnosis. However, even among these reports figures vary widely, Watt and Foushee reporting only 1% and Freeman 17% of nodular goiters as malignant. Factors of preselection by the patient and by the referring physician obviously increase the incidence of cancer in a series reported by a surgeon who operates on all patients.[16, 35, 46, 50, 55] These factors led Sokal [50-52] to conclude that the incidence of cancer is probably highest in toxic goiters and that an estimated incidence in nontoxic nodular goiter would be 0.2%. Crile [15] stated that if the incidence of palpable thyroid nodules in persons in the Great Lakes region were 5%, and the incidence of cancer in these nodules 8%, then the "absurd conclusion" would be that in Cleveland (population one million), 4,000 people would be "walking the streets" with thyroid cancer. Based on their own data, Crile and Dempsey [16] indicated that over 3% of nontoxic solitary thyroid nodules are undiagnosed cancers, or that there is only one chance in 6,675 that removal of a nontoxic solitary nodule will give protection against death from thyroid cancer.

The clinician must know the accuracy of nonoperative diagnosis, but here again there are various opinions. In the series of Shimaoka *et al.*,[46] only 2% of 202 thyroid lesions classified clinically as benign were proved to be malignant, while 28% of 18 "suspected of cancer" and 53% of 15 "probably cancer" were so proved. Similarly, 27 of 30 malignant tumors in Crile and Dempsey's [16] series were diagnosed preoperatively and two others were suspected; 20 of 507 benign nodular goiters were suspected of being malignant and none

were diagnosed before operation. Only 55% of cancers reported by Beahrs, Pemberton and Black [1] were thought clinically to be malignant, as were only 27 of Cattell and Colcock's [8] 78 cases. Of Cavanagh's [9] 27 cases, not only were 16 not suspected clinically but the surgeon, at operation, thought that 17 were benign. In the series of Cole, Slaughter and Rossiter,[12] 21% of carcinomas were diagnosed preoperatively, another 21% diagnosed at operation and 58% first identified in the surgical pathology laboratory. Even when a single palpable nodule is suspected of being malignant, it may turn out to be benign, with cancer in another nonpalpable focus, as in 14 cases reported by Block, Brush and Horn.[3] Although malignant tumors evident to the clinician are further advanced and warrant the poorest prognosis, even those first diagnosed by the pathologist can be fatal; in Ward's series,[58] 5-year survival was 20% if cancer was diagnosed preoperatively, 40% if discovered at operation, and 80% if first found by the pathologist. Similarly, 10 of 32 cases of "occult sclerosing carcinoma of the thyroid" reported by Klinck and Winship [32] had metastasized before the primary tumor was discovered, although no deaths were reported after a short follow up. Of 252 consecutive patients treated surgically for papillary carcinoma of the thyroid at Memorial Hospital (this series does not include patients with 'incidental" cancers discovered at thyroidectomy for benign disease), 19% presented with tumor in cervical lymph nodes and no palpable primary lesion.[54]

New technics offer some hope of improving clinical diagnoses. By using the radioactive iodine screen, Meadows [34] found that cancer was present in 58% of "cold" nodules but in only 4.7 to 6.6% of "hot," "warm" and "cool" nodules. Greene, Piercy and Singer [20] found no cancer in 54 "hot" and "neutral" nodules, while 20% of 109 "cold" nodules were definitely malignant and 6% probably so. Even authors who are enthusiastic about this technic admit that it is far from reliable in an individual case. Needle biopsy also has advocates. In 18 of 23 patients biopsied preoperatively by Heimann and Schnurer,[23] the diagnosis was correct, but in a larger series only 77% of biopsy specimens were adequate for diagnosis. In a still larger series of biopsied and surgical removed thyroids reported by Boehme *et al.*,[4] the accuracy of final diagnosis by needle biopsy was only 52% (and only 31% for carcinomas). These authors recommend needle biopsy only for confirmation of a suspected diagnosis of lymphocytic thyroiditis, believing (as do the present authors) that it may be more harmful than helpful in cancer. Thus, even with refined technics, certain lesions remain indistinguishable from cancer after clinical evaluation; Hill *et al.*[25] list these as cysts, hemorrhage into an adenoma or nodule, calcified lesions, fibrosis, "inactive" colloid nodules and "nodular thyroiditis."

Unless the clinician is willing to follow the dictum of Hinton and Lord [26] and Glass *et al.*[19] and recommend total thyroidectomy for all multiple nodular goiters and total lobectomy for all single nodules (a task limited by problems of space and manpower, if nothing else), he must choose a course [20, 25, 34, 43, 46, 57, 58] dictated by the incidence of thyroid carcinoma and by an estimate of its metastasizing and killing potential. Although metastases [50-52] and lethality [57] are said to be minimal by some authors, in most series of surgically diagnosed and treated thyroid carcinomas there is a significant number of deaths and of patients living with metastases if the follow-up period is longer than 5 years.[8, 11, 27, 58, 64] The discrepancy between frequency of surgical pathologic and autopsy pathologic diagnoses of thyroid cancer has been interpreted to indicate that fewer patients die with thyroid carcinoma than are diag-

nosed as having the disease during life. Both Willis[62] and Morganstern and Tiber[36] reported surgical pathologic/postmortem diagnostic ratios for thyroid carcinoma of 8:1. In 5 years preceeding the present study at the Yale-New Haven Hospital, this ratio was 10:1 (31 thyroid cancers diagnosed surgically, 3 at autopsy). Several authors[8, 11, 13, 62] attribute the discrepancy to the fact that most patients with thyroid cancer do not die in hospitals and are not autopsied, but Sokal[49] has shown (at least for New Haven, London and San Francisco) that the percentage of autopsies on patients dying with thyroid cancer is higher than that for many other types of malignant disease. In addition, Morganstern and Tiber[36] showed that the ratio of 8:1 surgical/postmortem for thyroid cancer in Los Angeles is matched by that for cancers of kidney, colon and breast, while uterus (6:1) is not dissimilar, and only stomach (3:1) and lung (2:1)—tumors which are very rarely cured—have significantly lower ratios. The reported low incidence of thyroid carcinoma at autopsy is partly due to the infrequency of careful examination of this organ at routine autopsy.[45, 47] In several large series of routine autopsies thyroid cancer is reported in 193 of 240,000 autopsies,[47] one per 429,[17] six in 2,185,[45] five in 18,668,[56] 13 in 3,868,[63] and 12 in 9,700.[49] The last figures, reported by Sokal, are for the period of 1917–1952 in our own hospital, and we can add three primary malignant tumors in 3,965 routine autopsies performed from 1959 to 1964. The overall average incidence of thyroid cancer at the routine autopsy is 0.08%.

This average changes however when consecutive autopsies in which special attention was paid to the thyroid are reported. Morganstern and Tiber,[36] in a retrospective analysis of about 2,000 such autopsies, found 32 thyroid cancers, an incidence of 1.6%. Correa and Castro[14] found one cancer in 250 cases, Hazard and Kaufman[22] three in 429 cases—both in studies of thyroid lesions not primarily neoplasms. In studies similar to the present one, Brierre and Dickson[6] found four cancers in 100 glands, Hull[30] three in 221, Queen[44] 20 in 1,217, and Morganstern, Bennett and Woolner[37] 28 in 1,000. The overall average incidence, including the present series of eight carcinomas in 300 thyroids, is 1.79%.

These data suggest that: 1) Thyroid cancer can be found about 20 times more frequently at autopsy if carefully searched for. 2) The 8:1 ratio between surgical and postmortem material is illusory for thyroid cancers (and perhaps for certain others as well). During the period in which eight thyroid cancers were diagnosed at autopsy, only three were diagnosed in the surgical pathology section. 3) Since 1.79% of people dying of all causes harbor thyroid carcinoma, a similar percentage of the general population presumably harbors the same tumor. (Fewer than 20% of 99 tumors used to compute this incidence were responsible for the death of the patient,[48] and therefore 80% of these patients did harbor clinically unsuspected tumors immediately prior to death.) These figures hold only for an older population, those dying in hospital and coming to autopsy. 4) If more than 1% of persons not suspected of having thyroid disease worthy of operation can be shown to have carcinoma of the thyroid, a greater proportion of patients referred to the surgeon can be expected to have cancer.

Summary

Rather than a rare finding at autopsy as previously claimed, carcinoma of the thyroid (usually unsuspected clinically) has been found in 1.79% of unselected cases. This is more than 20 times the incidence observed at routine autopsy (0.08%) in which examination of thyroid is incomplete or not included. Case reports in the literature confirm the experience of

the authors that a small but significant proportion of clinically occult thyroid carcinomas can result in widespread metastases and death. Patients with thyroid nodules, whether single or multiple, should be evaluated for the presence of cancer; those patients not treated operatively, and those in whom a small non-metastasizing carcinoma is discovered at operation, should be followed for many years.

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